Message

From: Nesci, Kimberly [Nesci.Kimberly@epa.gov]
Sent: 3/13/2018 3:08:51 PM
To: Echeverria, Marietta [Echeverria.Marietta@epa.gov]
Subject: FW: Request for EDSP background briefing

From: Blankinship, Amy
Sent: Monday, February 26, 2018 8:48 AM
To: Steeger, Thomas <Steeger.Thomas@epa.gov>; Nesci, Kimberly <Nesci.Kimberly@epa.gov>
Cc: Holmes, Jean <Holmes.Jean@epa.gov>
Subject: RE: Request for EDSP background briefing

Hi Kimberly,

In general, I agree with what Tom has written (a few additional notes in green below). I will get an invite on the calendar for 30 minutes so we can discuss any remaining questions you may have (it's tough to get you all at the same time that isn't a lunch meeting).

Amy

From: Steeger, Thomas
Sent: Friday, February 23, 2018 8:45 AM
To: Nesci, Kimberly <Nesci.Kimberly@epa.gov>; Blankinship, Amy <Blankinship.Amy@epa.gov>
Cc: Holmes, Jean <Holmes.Jean@epa.gov>
Subject: RE: Request for EDSP background briefing

A few initial thoughts (in red) for your consideration.

From: Nesci, Kimberly
Sent: Thursday, February 22, 2018 4:27 PM
To: Blankinship, Amy <Blankinship.Amy@epa.gov>; Steeger, Thomas <Steeger.Thomas@epa.gov>
Cc: Lowit, Anna <Lowit.Anna@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Holmes, Jean <Holmes.Jean@epa.gov>
Subject: Request for EDSP background briefing

Amy and Tom,

Thanks for all the information in Anna's EDSP meeting today. Before Anna schedules the follow-up meeting, and if it's OK with Jean, can you please schedule a 30 minute briefing for me on some of the basics of EDSP as it relates to eco? I'm piecing things together, but I think I need some historical context. Here are my general questions, as a starting point:

- I understand the following assays were the ones chosen to address this for non-mammalian species
  - Fish short-term reproduction (FSTRA) Tier 1
  - Amphibian metamorphosis, Tier 1
  - Avian Two-Generation Toxicity Test in the Japanese Quail Tier 2; however, we tend to rely on the current avian reproduction studies.
  - Medaka Extended One Generation Reproduction Test (MEOGRT) Tier 2
  - Larval Amphibian Growth and Development Assay (LAGDA) Tier 2; doesn't extend to sexual maturity/reproduction.
- Why we chose these assays The battery of Tier 1 and Tier 2 assays were a collective approach that extended well beyond EFED staff members over many years.

- What they tell us (EPA developed guidance as well as standard evaluation protocols for how each of the *in vitro* and *in vivo* Tier 1 assays provide specific lines of evidence in determining whether a chemical has the potential to/can impact estrogen, androgen and/or thyroid signaling pathways). These individual lines of evidence are then considered collectively through a weight-of-evidence analysis.
- Briefly, how they're conducted. EPA guidance documents provide very detailed information on the conduct and interpretation of the each study; highly standardized data evaluation record (DER) templates have also been developed for recording data from each of the studies. These DERs were finalized after the weight-of-evidence analysis had been completed across the full battery of 11 assays and other scientifically relevant information. [All SEPs/guidelines and DERs are publicly available]
- Whether they're used in risk assessment (we discussed this a bit today) and/or inform decision making. If they are, how many risk assessments/how often do we use them, and how have we used them? (Not a comprehensive evaluation of this; just generally what we've done.) The Tier 1 tests were not [initially] intended for use in risk assessment since the tests do not typically contain sufficient replication [or number of test concentrations] to support development of robust hypothesis testing and treatment-response curves. They have been used (typically qualitatively) to variable extents in risk assessment though. The Tier 2 assays are however intended to be used to support risk assessment; however, effects observed in those tests cannot necessarily be prescribed to result from direct effects on endocrine signaling pathways [my understanding is they were envisioned to be used along with the Tier 1 mechanistic data to better understand potential interactions]. As you know, each of our preliminary risk assessment chapters in support of Registration Review note whether the chemical was or was not part of the initial group of chemicals tested in the Tier 1 battery. As such, if chemical teams are aware of their chemical being tested, they should review the weight-of-evidence analysis for the chemical; however, the chapter should not speculate on whether the chemical is an "endocrine disruptor". Since the Tier 1 and 2 assays are very well defined testing protocols, some EFED staff have recommended these tests *in lieu* of fish full lifecycle tests or if there were uncertainties regarding potential effects on amphibians. In these case, the protocols are changed to increase the number of replicates and spacing is adjusted between treatment levels to more accurately define the concentration-response relationship.
- Why the high throughput assays and computational models mentioned in Anna's slides can or can't replace the study, for screening purposes. There are a lot of chemicals which will be subject to EDSP testing and it quickly became clear that they all couldn't be subject to the initial battery of 11 tests in vitro/in vivo tests since the resources needed to conduct and review the studies would be enormous. The high through-put assays (HTPA) help reduce the need for animal testing and provide a rapid means of assessing estrogen and androgen signaling modalities. The thyroid pathway is more challenging and HTPA are still under development [along with finishing up the steroidogenesis pathway]. Many of the assays provide highly mechanistic information (*e.g.*, molecular initiating events; MIE) and may not be able to capture potential impacts at key events down-stream of the MIE. The assays have tended to be mammalian centric and there is uncertainty as to the extent to which they may reflect effects on wildlife if modes of action are not well conserved across taxa. Also, some chemicals may undergo bioactivation or may conversely be rapidly deactivated, and it is uncertain whether the in vitro assays would capture this. The major concern is whether the screen will be sufficiently robust to reduce the likelihood of making a Type II error, *i.e.*, concluding that there is not effect when there is. From an EFED perspective though, we are not particularly interested in the mode of action of a chemical (although the information is useful for characterization purposes). Rather, we are interested in measurement endpoints that are quantitatively linked to assessment endpoints of impaired survival, growth and/or reproduction and are known to impact populations. Our current testing requirements provide that information without having to know whether the effect was the result of a direct effect on an endocrine pathway. However, to be true to the original intent of the EDSP (FQPA) requirement, we want to provide due diligence to answering the question as to whether a chemical has the potential to impact E, A or T signaling pathways. I think we all recognize though that the philosophy of replacing *in vivo* tests with *in vitro* assays is directionally correct so that resources can be better directed to where they are most needed. However, we have a responsibility to ensure that we do not forsake accuracy for expediency.

Thanks in advance, and please invite Anna and Jean (with Marietta as optional), too.

Kimberly

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